Tumour assessment in advanced melanoma: value of FDG-PET/CT in patients with elevated serum S-100B

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Abstract: PURPOSE: To evaluate the usefulness of PET/CT in melanoma patients with an elevated serum S-100B tumour marker level. METHODS: Out of 165 consecutive high-risk melanoma patients referred for PET/CT imaging, 47 had elevated (>0.2 microg/l) S-100B serum levels and a contemporaneous 18F-FDG PET/CT scan. PET/CT scans were evaluated for the presence of metastases. To produce a composite reference standard, we used cytological, histological, MRI and PET/CT follow-up findings as well as clinical and S-100B follow-up. RESULTS: Among the 47 patients with increased S-100B levels, PET/CT correctly identified metastases in 38 (30 distant metastases and eight lymph node metastases). In one patient with cervical lymph node metastases, PET/CT was negative. Eight patients had no metastases and PET/CT correctly excluded metastases in all of them. Overall sensitivity for metastases was 97% (38/39), specificity 100% (8/8) and accuracy 98% (46/47). S-100B was significantly higher in patients with distant metastases (mean 1.93 microg/l, range 0.3-14.3 microg/l) than in patients with lymph node metastases (mean 0.49 microg/l, range 0.3-1.6 microg/l, p=0.003) or patients without metastases (mean 0.625 microg/l, range 0.3-2.6 microg/l, p=0.007). However, 6 of 14 patients with a tumour marker level of 0.3 microg/l had no metastases. CONCLUSION: In melanoma patients with elevated S-100B tumour marker levels, FDG-PET/CT accurately identifies lymph node or distant metastases and reliably excludes metastases. Because of the significant number of false positive S-100B tumour marker determinations (17%), we recommend repetition of tumour marker measurements if elevated S-100B levels occur before extensive imaging is used.

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ORIGINAL ARTICLE

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Conclusion In melanoma patients with elevated S-100B tumour marker levels, FDG-PET/CT accurately identifies lymph node or distant metastases and reliably excludes metastases. Because of the significant number of false positive S-100B tumour marker determinations (17%), we recommend repetition of tumour marker measurements if elevated S-100B levels occur before extensive imaging is used.

Keywords Melanoma · PET/CT · S-100B · Metastases

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Introduction

^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is increasingly used to image patients with melanoma [1]. Recent publications have demonstrated that FDG-PET/CT has a high accuracy for N- and M-staging in melanoma patients and is superior to PET alone, CT alone or conventional imaging methods [2, 3]. Because FDG-PET/CT is still a relatively expensive technique with limited availability, it is not practicable to use PET/CT as a screening tool in all melanoma patients. Thus, it is very important to identify groups of patients and clinical situations where PET/CT has a diagnostic and therapeutic impact.

Long survival of patients with malignant melanoma has been reported after surgery of regional lymph node metastases or solitary distant metastases. In many institutions, patients with multiple distant metastases are included in clinical trials and treated with immuno-chemotherapy [4]. Thus, accurate staging of melanoma patients with exact localisation of metastases is crucial for therapy planning.

Serum S-100B has been reported to be a reliable tumour marker in melanoma, reflecting the tumour burden [5], and it seems to be useful in monitoring therapy [6, 7]. Further, it has been shown that S-100B can be used as a prognostic marker in melanoma patients [8–12]. As demonstrated in colon cancer and prostate cancer, PET imaging can be very helpful in localising recurrences in patients with elevated or increasing tumour marker levels [13–16].

The aim of this study was therefore to assess the value of FDG-PET/CT in melanoma patients with elevated (>0.2 μg/l) S-100B tumour marker levels.

Materials and methods

Patients

Our institution is a teaching and tertiary care hospital and a major referral site for patients with malignant melanoma.

We received approval from our institutional review board to undertake this study.

One hundred and sixty-five consecutive melanoma patients followed up according to updated Swiss melanoma guidelines [17] were referred for FDG-PET/CT imaging between January 2005 and January 2006. Retrospectively, from among this population, 47 patients (27 women, 20 men; mean age 58.4 years, range 20–83 years) who fulfilled the following criteria were selected: (1) diagnosis of high-risk melanoma (Breslow tumour thickness >4 mm, Clark level III or IV or known resected metastases in the case history); (2) elevated S-100B levels (>0.2 μg/l); (3) FDG-PET/CT and S-100B measurement within an interval of not more than 2 weeks; (4) no treatment between PET/CT and tumour marker measurement; (5) no systemic therapy before the PET/CT investigation. Informed consent was obtained from all patients before they were investigated.

Determination of S-100B

The determination of serum S-100B was done with a commercially available immunoassay (ELISA) kit (Sangtec 100 ELISA, Dia Sorin Inc, Stillwater, NM, USA) according to the manufacturer's instructions. Cut-off was determined to be 0.2 μg/l (the 95th percentile of blood donor samples). Values ≥0.3 μg/l were considered suspicious for melanoma metastases. The detection limit is 0.03 μl/l (BO+3SD). Intra-assay and inter-assay precision was estimated by analysis of variance (ANOVA). The within-run and total imprecision is <10%. The evaluation of S-100B was introduced in our clinic in 1992.

PET/CT imaging

All the data were acquired on a combined PET/CT in-line system (Discovery LS or Discovery ST, GE Health Systems, Milwaukee, WI). These dedicated systems integrate a PET scanner (GE Advance Nxi, GE Health Systems, Milwaukee, WI) with a multislice helical CT (LightSpeed plus or Lightspeed 16; GE Health Systems, Milwaukee, WI) and permit the acquisition of co-registered CT and PET images in one session.

Patients fasted for at least 4 h prior to the scanning, which started 60 min after the injection of 370–400 MBq of ^{18}F-FDG. All patients were tested for a normal glucose level [range 80–120 mg/dl (4.4–6.7 mmol/l)] before scanning. Patients with elevated glucose levels were rescheduled and scanned with normal glucose levels. Oral CT contrast agent (Micropaque Scanner, Guerbet AG, Aulnay-sous-bois, France) was given 15 min before the injection of ^{18}F-FDG. Patients were examined in the supine position. No intravenous contrast agent was given. Initially, the CT scan was acquired starting from the level of the head using the following parameters: 40 mAs, 140 kV, 0.5 s/tube rotation, slice thickness 4.25 mm, scan length 867 mm, data acquisition time 22.5 s. The CT scan was acquired during breath holding in the normal expiratory position.

Immediately following the CT acquisition, a PET emission scan was acquired with an acquisition time of 3 min per cradle position with a one-slice overlap in 2D mode (matrix 128×128). The eight to nine cradle positions starting from the head to the knees resulted in an acquisition time of approximately 24–27 min. In the patients with primary tumours of the lower extremities, the scanning of the lower legs was added. The CT data were used for attenuation correction of the PET datasets and the images were reconstructed using a standard iterative algorithm (OSEM). The acquired images were viewed with software providing multiplanar reformatted images of PET alone, CT alone and fused PET/CT with linked cursors using a Xeleris workstation (GE Health Systems, Milwaukee, WI).

PET/CT imaging was performed according to the recently published procedure guideline for tumour imaging with ^{18}F-FDG PET/CT version 1.0 [18].

PET/CT interpretation

The images were reviewed and analysed by two experienced nuclear radiology physicians without knowledge of the results of other imaging studies or the level of serum S-100B. A consensus was reached on every observed lesion. The PET

Table 1 Patient characteristics, S-100B values and results of PET/CT imaging

Pat. no.	Gender	Age (yrs)	Breslow thickness (mm)	Serum S-100B (μg/l)	PET/CT	Ref. standard	Therapy	Localisation of mets.[a]
1	F	49	?	0.3	No mets	No mets	No	–
2	M	45	3.00	0.3	No mets	No mets	No	–
3	F	52	1.50	0.3	No mets	No mets	No	–
4	F	83	?	0.3	No mets	No mets	No	–
5	M	67	2.75	0.3	No mets	No mets	No	–
6	F	43	?	0.3	No mets	No mets	No	–
7	F	33	1.90	0.6	No mets	No mets	No	–
8	F	74	5.50	2.6	No mets	No mets	No	–
9	F	68	1.20	0.3	LN mets	LN mets	OP	LN (iliac)
10	M	36	?	0.3	LN mets	LN mets	OP	LN (axilla)
11	F	67	4.00	0.3	LN mets	LN mets	OP	LN (inguinal)
12	F	73	3.50	0.3	LN mets	LN mets	OP	LN (inguina)
13	F	59	?	0.3	LN mets	LN mets	OP	LN (inguinal)
14	M	72	5.80	0.3	LN mets	LN mets	OP	LN (cervical)
15	F	77	4.60	0.4	No mets	LN mets	OP	LN (cervical), probable bone met
16	M	69	1.10	0.6	LN mets	LN mets	OP	LN (axilla)
17	F	58	3.30	1.6	LN mets	LN mets	OP	LN (inguinal and popliteal)
18	M	73	8.00	0.3	Dist mets	Dist mets	Chemo	Dist LN
19	M	50	4.30	0.3	Dist mets	Dist mets	Chemo	Liver, bone, LN
20	M	66	3.70	0.4	Dist mets	Dist mets	Chemo	Lung, adrenal, soft tissue, dist LN
21	M	70	3.45	0.4	Dist mets	Dist mets	Chemo	Liver
22	M	59	?	0.5	Dist mets	Dist mets	OP	Bone (clavicle)
23	F	49	1.80	0.5	Dist mets	Dist mets	Chemo	Lung, bone, dist LN, soft tissue
24	M	42	3.65	0.5	Dist mets	Dist mets	Chemo	Lung, liver, soft tissue
25	F	47	1.20	0.5	Dist mets	Dist mets	Chemo	LN (inguinal), lung
26	F	79	?	0.5	Dist mets	Dist mets	Chemo	Soft tissue
27	F	68	11.00	0.5	Dist mets	Dist mets	Chemo	Lung, liver
28	F	46	1.70	0.6	Dist mets	Dist mets	Chemo	Lung, dist LN
29	F	81	2.50	0.6	Dist mets	Dist mets	Chemo	Lung
30	M	71	5.30	0.6	Dist mets	Dist mets	Chemo	Lung, liver, soft tissue, dist LN
31	F	43	2.75	0.6	Dist mets	Dist mets	Chemo	Liver, bone, LN
32	F	20	2.10	0.6	Dist mets	Dist mets	Chemo	Liver, dist LN
33	M	66	4.50	0.6	Dist mets	Dist mets	Chemo	Lung, soft tissue
34	F	49	1.02	0.7	Dist mets	Dist mets	Chemo	Soft tissue, dist LN
35	F	70	8.00	0.8	Dist mets	Dist mets	OP	Intestine, dist LN
36	F	72	15.00	0.8	Dist mets	Dist mets	Chemo	Soft tissue
37	M	51	7.50	0.8	Dist mets	Dist mets	Chemo	Liver, lung, bone
38	M	56	6.00	0.9	Dist mets	Dist mets	Chemo	Liver, soft tissue, dist LN
39	M	53	?	0.9	Dist mets	Dist mets	Chemo, RT	LN (axilla), dist LN
40	F	47	1.30	0.9	Dist mets	Dist mets	Chemo	Lung, liver, brain
41	M	59	3.50	1.3	Dist mets	Dist mets	Chemo	Lung
42	F	41	6.50	1.7	Dist mets	Dist mets	Chemo	Lung, liver, adrenal, soft tissue
43	M	83	3.90	2.0	Dist mets	Dist mets	Chemo	Lung, soft tissue
44	F	49	0.94	4.2	Dist mets	Dist mets	Chemo	Lung, bone, brain, soft tissue
45	M	42	2.24	7.9	Dist mets	Dist mets	Chemo	Intestine, dist LN
46	M	67	1.40	12.6	Dist mets	Dist mets	Chemo	Lung, liver
47	F	52	?	14.3	Dist mets	Dist mets	Chemo	Liver, adrenal, dist LN

? Depth of the primary tumour not known, *M* male, *F* female, *dist mets* distant metastases, *LN mets* regional lymph node metastases, *dist LN* distant lymph node metastases (no regional LN mets), *OP* operative resection, *Chemo* chemotherapy, *RT* radiotherapy

[a] According to the reference standard

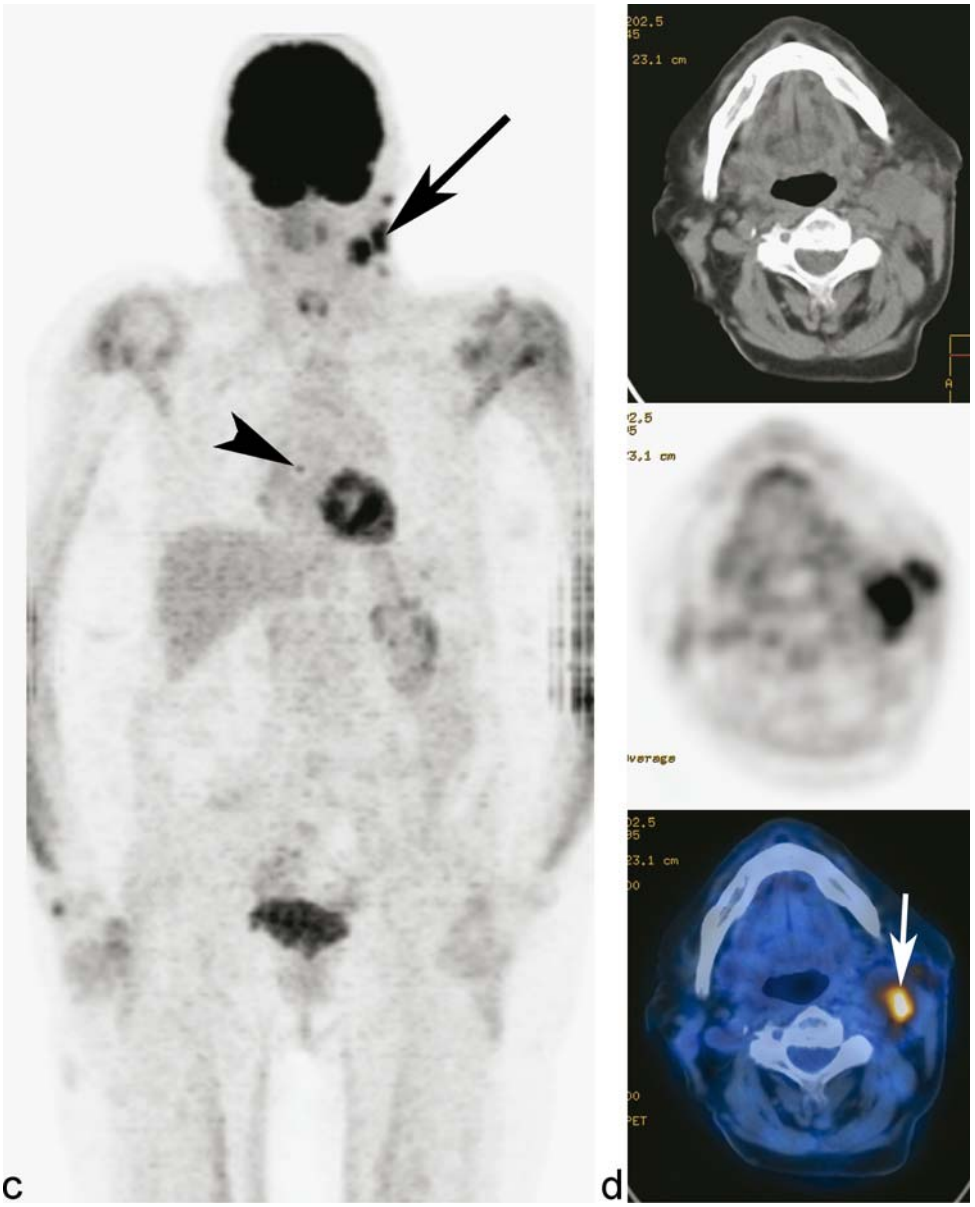
Fig. 1 A 77-year-old female patient with high-risk melanoma and elevated serum S-100B (0.4 μg/l). **a** MIP image and **b** axial images through the neck without evidence of metastases. There is elevated FDG uptake in both shoulders and the right patella (*arrows*) due to osteoarthritis. Contamination is present at the injection site of the left elbow (*arrowhead*). **c** MIP image 6 months later with increased FDG uptake in the cervical lymph nodes on the left side (*arrow*) and in the thoracic spine (*arrowhead*). **d** Axial images demonstrating that the elevated FDG uptake belongs to a level II lymph node on the left side (*arrowhead*). The cervical lymph node metastases were resected and confirmed histologically. MRI of the spine was inconclusive as it showed a small lesion in the transverse process

images and the corresponding CT images of the PET/CT study were analysed for the presence and nature of focal lesions with elevated FDG uptake. For all of the patients, the attenuation-corrected PET images were analysed. Lesions were interpreted as metastases if the FDG uptake was clearly greater than background. If a focal FDG-active lesion was detected, the exact anatomical localisation was determined on the fused PET/CT images. Lesions with ^{18}F-FDG uptake in physiological sites or benign variants, e.g. muscles, brown fatty tissue or pulmonary infiltrations, were determined as benign. CT images were additionally analysed concerning FDG-inactive soft tissue dense lesions without calcifications, especially in the lungs and subcutaneous fatty tissue. Lesions suspicious for metastases according to the established morphological CT criteria known from diagnostic radiology were also diagnosed as metastases.

Reference standard

Lymph node or distant metastases were confirmed by a histopathological or cytological examination or other imaging modalities such as magnetic resonance imaging (MRI), PET/CT follow-up and clinical follow-up for a minimum of 6 months (range 6–18 months in all patients),

Fig. 1 (continued)



including follow-up measurement of the serum S-100B. A false negative PET/CT diagnosis was determined if another imaging method (superior for the investigated region, such as brain MRI) showed metastases or if clinical findings raised the suspicion of metastases which were then proven by histology. A false positive PET/CT diagnosis was determined if histology of the lesion and/or clinical and PET/CT follow-up (complete disappearance of focal FDG-active lesion without therapy) ruled out metastases. FDG-negative, non-calcified lesions (for example in the lung) were determined as false positive if there was no change in lesion number or size on the follow-up PET/CT examinations 3 or 6 months later and no clinical suspicion of metastases arose >6 months after the scan.

Statistical analysis

The recorded data were entered into a worksheet (Excel; Microsoft, Redmond, Washington). Data analysis was performed on a patient basis. SPSS (version 11; 2002; SPSS Inc.) was used for statistical analysis. Sensitivity, specificity and accuracy are presented with exact 95% confidence intervals (Scientific Tables by Geigy, Volume on statistics, 8th edition, Basle 1980). The Mann-Whitney test with Bonferroni correction was used to assess statistical differences in serum S-100B values in patients without metastases, with regional lymph node metastases and with distant metastases. Thus, $p<0.017$ was considered to indicate a significant difference.

Results

Patient characteristics are summarised in Table 1. Thirty (64%) of the 47 patients had distant metastases, nine (19%) had regional lymph node metastases and eight (17%) patients had no metastases. Of patients with distant metastases, 20 had their findings confirmed by histology, four by cytology and six by MRI, PET/CT follow-up and clinical follow-up. All nine patients with regional lymph node metastases had their diagnoses confirmed histologically following surgical resection.

PET/CT correctly detected distant metastases in all 30 patients. PET/CT identified lymph node metastases in eight patients and missed multiple level II and III cervical lymph node metastases and a probable vertebral spinal metastasis in one patient (no. 15., Fig. 1). Eight patients had no metastases and PET/CT correctly excluded metastases in all these patients. Overall sensitivity for metastases was 97% (38/39) [95% CI, 87–100%], specificity 100% (8/8) [63–100%] and accuracy 98% (46/47) [89–100%]. Serum S-100B was significantly higher in patients with distant metastases (mean 1.93 μg/l, range 0.3–14.3 μg/l) than in patients with regional lymph node metastases (mean 0.49, range 0.3–1.6, p=0.003) or patients without metastases (mean 0.625, range 0.3–2.6, p=0.007); however, there was considerable overlap between each of the subgroups. There was no statistical significant difference in S-100B values between patients with lymph node metastases and patients without metastases (p=0.86).

Six (42.9%) of the 14 patients with a weakly elevated tumour marker of 0.3 μg/l had no metastases, six (42.9%) had regional lymph node metastases and two (14.3%) had distant metastases. An example of a patient with distant metastases and elevated S-100B is shown in Fig. 2.

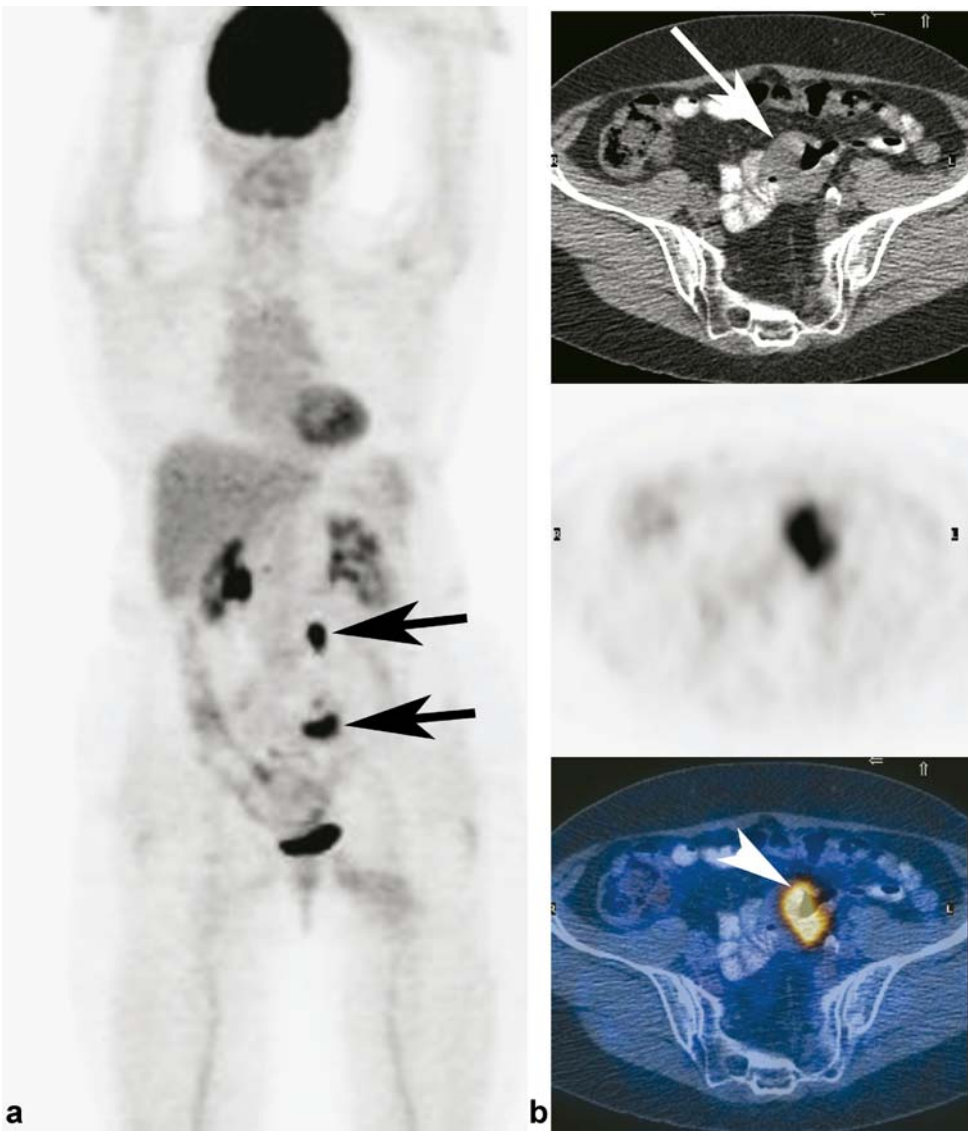


Fig. 2 A 70-year-old female patient with high-risk melanoma and elevated S-100B (0.8 μg/l). **a** MIP image demonstrating two focal FDG-active lesions in the abdomen (*arrows*). **b** On the axial images one FDG-active lesion (*arrowhead*) corresponds to wall thickening (*arrow*) in the small intestine. The lesion was resected and histology confirmed the PET/CT diagnosis of small intestine metastases

Eight patients had "false positive" S-100B tumour markers (Table 2). In three patients (nos. 5, 6 and 7) with S-100B values of 0.3–0.6 μg/l we found a history of brain operation for melanoma metastases (2 weeks, 6 months and 8 years previously). One patient (no. 8) with a normal S-100B value 6 months prior to the study showed an increase in S-100B to 2.6 μg/l without clinical evidence of metastases. PET/CT at the timepoint of the elevated tumour marker and PET/CT follow-up investigations after 2, 6 and 18 months were normal. S-100B levels measured 2 weeks and 6 and 18 months after the pathological value were normal (0.1–0.2 μg/l). Similarly, in the remaining four patients (nos. 1–4) we found no explanation for an elevated S-100B value in the history. The follow-up S-100B measurements, PET/CT scans and clinical investigations remained without evidence of metastases. In one patient (no. 37) with an S-100B of 0.8 μg/l, PET/CT only detected a solitary metastasis in a vertebral body of the thoracic spine (Fig. 3). MRI and contrast-enhanced CT, performed in the following week, showed disseminated small liver and bone metastases, so that PET/CT as correct in the diagnosis of distant metastasis but severely underestimated the extent of metastases. Twelve patients had lung metastases. Lung metastases were FDG active in eight patients and FDG inactive in four patients. In these four patients the lung metastases were only detected by the additional interpretation of the lung window of the CT examination. Two patients had brain metastases. They were detectable in both patients with PET/CT because of elevated FDG uptake compared with normal brain tissue in one patient and because of additional bleeding in the other patient. Additionally in both patients perifocal vasogenic oedema was present in CT images.

Discussion

To our knowledge, this is the first study to describe the value of integrated PET/CT imaging in the follow-up of melanoma patients with elevated S-100B tumour marker levels. The results demonstrate that FDG-PET/CT is very useful in this selected group of melanoma patients with a high risk for the presence of metastases. FDG-PET/CT reliably discriminates between patients with distant metastases, which are usually treated with chemotherapy, and patients with regional lymph node metastases, which are often treated by surgery. If an S-100B level of 0.3 μg/l or more is considered pathological, there is a significant number of patients with false positive S-100B. FDG-PET/CT excluded metastases correctly in all of these patients. One of our study patients with a slightly elevated S-100B level (0.4 μg/l) had a normal PET/CT scan. Cytologically proven cervical lymph metastases were diagnosed 5 months after the FDG-PET/CT examination. This situation was interpreted as a false negative PET/CT diagnosis. It has been shown in several studies that FDG-PET/CT has limitations in the detection of microscopic lymph node metastases. FDG-PET was compared with sentinel node biopsy in a prospective study. The sensitivity of FDG-PET was 16.7% and the specificity, 95.8%. [19]. Thus, sentinel lymph node biopsy remains the standard and is clearly superior to FDG-PET(/CT) in detecting regional lymph node metastases [20, 21].

FDG-PET reliably detects lymph node tumour deposits with a volume larger than 80 mm^3, but sensitivity falls rapidly below this value because of partial volume effects that reduce the FDG signal [22]. All lymph node metastases

Table 2 History and follow-up of eight patients with false positive S-100B tumour marker levels

Pat. no.	Initial serum S-100B (μg/l)	History	Serum S-100B (μg/l) at follow-up	PET/CT follow-up	Clinical follow-up
1	0.3	Inconspicuous	0.2/3 mo; 0.2/5 mo	No mets after 6 mo	No evidence of mets after 8 months
2	0.3	Inconspicuous	0.0/3 mo; 0.0 /12 mo	No mets after 12 mo	No evidence of mets after 12 months
3	0.3	Inconspicuous	0.2/7 mo	No	No evidence of mets after 12 months
4	0.3	Inconspicuous	0.2/5 mo; 0.2/15 mo; 0.1/27 mo	No mets after 6 mo	No evidence of mets after 27 months
5	0.3	2 wk after resection of brain metastases	No	No	Died 6 wk after PET due to postop. infection; mets cannot be excluded
6	0.3	8 yr after resection of brain metastases	0.1/6 mo; 0.2/12 mo; 0.1/18 mo	No mets after 6 mo/ 18 mo	No evidence of mets after 18 months
7	0.6	6 mo after resection of brain metastases	0.1/6 wk; 0.1/3 mo; 0.0/6 mo; 0.1/12 mo; 0.1/24 mo	No mets after 6 mo/ 12 mo/18 mo/ 24 mo	No evidence of mets after 24 months
8	2.6	Inconspicuous	0.2/2 wk; 0.1/6 mo; 0.2/18 mo	No mets after 2 mo/ 6 mo/18 mo	No evidence of mets after 24 months

wk weeks, *mo* months, *yr* years, *mets* metastases

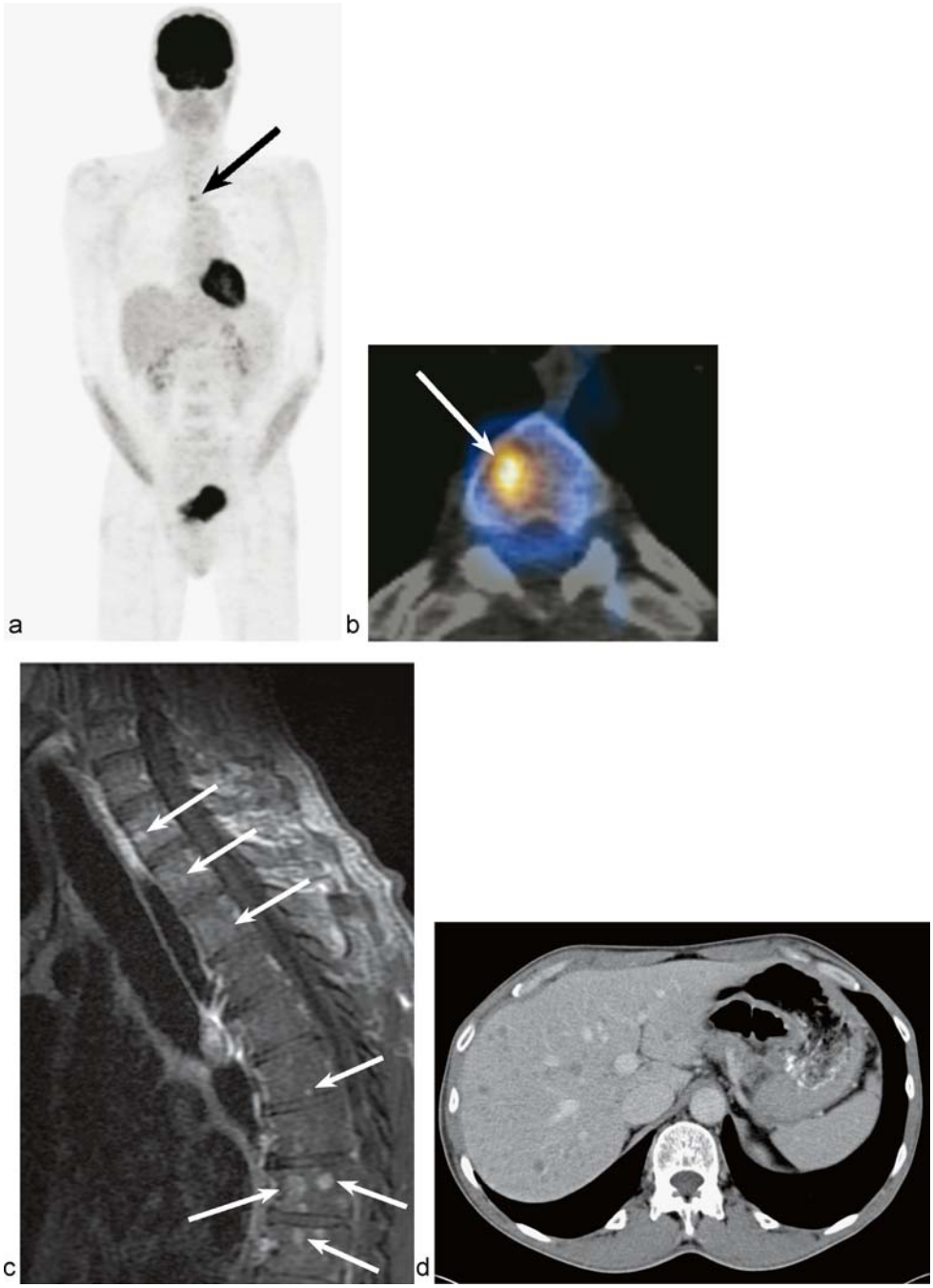


Fig. 3 A 51-year-old male patient with high-risk melanoma and elevated S-100B (0.8 μg/l). PET (MIP image, **a**) and axial fused PET/CT image (**b**) show a solitary bone lesion in a thoracic vertebral body (*arrow*). MRI (sagittal contrast-enhanced fat-saturated image, **c**) shows multiple disseminated enhancing bone metastases (*arrows*) in the whole spine. CT (axial contrast-enhanced image, **d**) detects disseminated small liver metastases

detected with PET/CT in our patients measured more than 6 mm. We know from other studies that some patients with microscopic or occult lymph node metastases have normal S-100B values. Reinhardt et al. reported that 8 of 11 patients with lymph node metastases and no distant metastases had normal S-100B values (all 0.1 μg/l) and only three had elevated levels (0.3, 0.9 and 1.6 μg/l). By contrast, all 13 patients with proven distant metastases had elevated S-100B values (range 0.3–23 μg/l) [23]. Bearing in mind the hypothesis that S-100B values are related to total tumour burden, it seems reasonable that if lymph node metastases lead to an elevated S-100B, the chance is very high that they will be detectable with FDG-PET/CT.

We also found a considerable number of false positive S-100B tumour marker determinations (17%; 95% CI, 6%–28%). There are various possible reasons for a false positive S-100B value: elevated S-100B levels have been observed after head trauma, subarachnoidal haemorrhage and stroke. It has been reported that S-100B reflects the extent of injury and the outcome of brain-injured patients [24, 25]. Furthermore, it indicates blood-brain barrier dysfunction [26, 27]. Molina et al. measured S-100B levels

in healthy people, patients with benign diseases and patients with malignancies, including patients with locoregional disease and advance diseases. All of the healthy people had normal S-100B values. Slightly elevated S-100B concentrations were found in 25% of individuals with benign diseases. Significantly higher S-100B serum levels were found in patients with liver cirrhosis or renal failure. Pathological S-100B serum levels were found in 22.5% of individuals with malignancies. The highest S-100B concentrations were found in patients with malignant melanomas. They concluded that "S-100 is a useful marker for melanoma, but abnormal levels of this tumour marker may be found in benign and malignant diseases associated with liver or renal injury" [26]. In three of our eight patients with false positive S-100B values we found brain operations in their past history. In one patient a melanoma brain metastasis had been resected 2 weeks before an S-100B level of 0.3 μg/l was measured. This patient died 6 weeks after the PET/CT due to postoperative infected subdural haematoma. In two other patients the brain operations could not explain the elevated S-100B level because the operations had been performed 6 months and 8 years previously. In the latter two patients no brain or other metastases developed at follow-up. In five of the eight patients with "false positive" tumour marker levels we found no explanation in the history or follow-up.

It is well known that PET has poor sensitivity in detecting brain metastases owing to the high physiological FDG uptake in the normal brain [28]. MRI is the imaging gold standard in the detection of brain metastases [29]. Among our patients we had no case in which PET/CT missed brain metastases; however, in patients with repeatedly elevated tumour markers and negative PET(/CT), additional brain MRI is strongly recommended.

A recently published study compared FDG-PET/CT imaging for N- and M-staging of 250 consecutive melanoma patients with PET alone and CT alone. The accuracy of PET/CT for M-staging was significantly higher than that of PET alone and CT alone (98% vs 93% and 84%). A change of treatment according to PET/CT findings occurred in 121 of the patients (48.4%). Interestingly, the authors pointed out that the most significant advantage of PET/CT in comparison to the single modalities PET and CT was observed in the detection of visceral metastases [2]. Performance of PET/CT in this study corresponds quite well with our results (overall accuracy 97.8%). Although we report a 100% specificity in this paper, we want to point out that false positive cases occur in our daily routine outside of this presented patient population.

The effect of chemotherapy in stage IV melanoma patients is still disappointing [30, 31]. Many patients with metastases are included in clinical trials where therapy response has to be assessed [32]. The data of Henze et al. support the value of serum S-100B as a clinical marker for monitoring response of metastatic melanoma during systemic therapies [6] but there are clear limitations in its sensitivity and specificity. We think that FDG-PET/CT may be very useful in therapy assessment of melanoma patients in a similar way to its use in patients with oesophageal, lung and head and neck cancers, but data are still very limited. In an ongoing study we plan to evaluate the behaviour of S-100B, standardised uptake value and total lesion glycolysis in stage IV melanoma patients treated with chemotherapy.

Our study has some limitations. As in all studies evaluating the accuracy of staging, the establishment of a standard of reference with which the method can be compared is difficult, because we cannot ethically justify obtaining histological proof of the diagnosis for all lesions identified. Nevertheless, we exercised great caution in establishing our standard of reference by using histopathological or cytological confirmation of the suspected metastases in 33/39 of patients (24 of 30 patients with distant metastases and all nine patients with lymph node metastases) and by confirming the findings with another structural imaging modality or with PET/CT and clinical follow-up.

We did not investigate whether the outcome of the patients correlated with the S-100B level. We know from other publications that there is a strong association between S-100B level and overall survival and that S-100B can be used as a prognostic marker [8, 9, 11, 12, 33]. Whether FDG-PET/CT can be used as an independent prognostic factor has to be investigated in further studies.

This is a retrospective study and has a selection bias because only patients with elevated S-100B values were included. We chose this selection because we were interested in the value of PET/CT in this particular clinical situation.

To avoid unnecessary PET/CT investigations in patients with false positive S-100B values, like other authors we recommend repeating the S-100B determination after 2–4 weeks if it is initially elevated in the absence of clinical evidence of metastases [34]. Further, we recommend that the S-100B measurements should be performed in the same laboratory always using the same method, thereby avoiding the bias associated with use of different assays [35]. Our results confirm that S-100B is not useful in melanoma patients after brain operation or trauma. Because FDG-PET/CT has been proven to be superior to PET alone or conventional imaging methods like CT or ultrasound [2, 36], we recommend FDG-PET/CT as the first imaging method in patients with repeatedly elevated S-100B.

In conclusion, our results indicate that integrated PET/CT imaging has a significant value in triaging melanoma patients with elevated S-100B tumour marker levels.

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